Remarks

Applicants enclose a fully executed Revocation of Power of Attorney with New Power of Attorney and Change of Correspondence Address. Applicants request that the mailing address for this case be changed to:

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Foster City, CA 94404
Attention: Intellectual Property

Claim 1 has been amended to recite that the tissues are not the same (basis at least the paragraph bridging pages 11 – 12 and the exemplary showings). Claim 14 is canceled.

Turning to the Office Action, claims 4 and 5 were objected to for use of certain acronyms. The claims have been amended to insert the meaning of the acronyms. This objection should now be moot.

Claim 12 was objected to for dependency on itself. This has been ameliorated by changing the dependency to claim 11. This rejection should now be moot.

Claim 7 was rejected under 35 U.S.C. 112(2) as being indefinite for the lack of antecedent basis for the term "amidate". This has been remedied by the recitation in claim 7 of the full terms "phosphonoamidate" and "phosphonoamidate/phosphonoester" (found in claim 6). This rejection should now be moot.

Claims 1-5, 9 and 14-16 were rejected under 35 U.S.C. 102(b) as being anticipated by Glazier et al. According to the examiner, Glazier et al. teaches a method of screening for antiviral activity of PMEA prodrugs on lymphatic tissue and liver tissue. Glazier also is said to disclose administering the prodrug to a target (infected) tissue and a control (uninfected) tissue, determining the antiviral activity of the prodrug on the tissues and selecting a prodrug having activity in the infected tissue that is greater than 10 times that in the non-infected tissue. The examiner supports his position with col. 36,

lines 35-48, col. 37, lines 5-22, columns 38 and 39 (tables), col. 39, lines 40-59 and col. 27, lines 34-35. Applicants respectfully traverse this rejection.

Applicants' claims require selecting a target tissue and a non-target tissue for a candidate therapeutic prodrug, administering the prodrug to these tissues and determining the relative activity of the prodrug in the tissues. The method can be conducted in vitro or in vivo. Applicants have amended the claims to recite that the tissues are different. None of the Glazier et al. disclosures are directed to this method.

Col. 36, lines 35-48 are merely a recitation of a conventional in vitro cell culture assay for antiviral efficacy. A single tissue type is used. An uninfected tissue and an infected tissue of the same type are not two different tissues as now set forth in the claims. Thus, this section of Glazier et al. fails to disclose the feature of a target tissue and a different non-target tissue.

Col. 37, lines 5 – 22 are not as relevant as col. 36, lines 35-48 since there is no control (uninfected) tissue apparent.

Col. 38-39 (Tables) appear to be no more relevant than the col. 36 disclosure. At most, these experiments are studies of prodrug activity on infected (EC50) and uninfected (CC50) cells of the same tissue type.

Col. 39, lines 4-59 deal with a study of the effect of prodrug on HSV infection in mice by assaying the viral titer in a target tissue (vaginal tissue). This disclosure fails to teach or suggest applicants' use of a different non-target tissue.

Col. 27, lines 34-35 teaches administering prodrug to TDT+ leukemia cells. There is no disclosure of a different non-target tissue.

The examiner did not refer to col. 41, lines 43-col. 42, lines 1-27. This disclosure relates to administration of a fluorescent prodrug to intact mice, but does not entertain the

concept of a therapeutic target and non-target tissue. While this disclosure does observe that various tissues were enriched for the prodrug, no attempt is made to harness this observation for the purpose covered by applicants' invention. In particular, no tissue was selected to be a "therapeutic" target. On the contrary, the purpose of the study in cols. 41-2 was to determine the effect of the prodrug on *all* tissues. As such, this disclosure in fact teaches away from the invention because Glazier et al. were presented with the biological information upon which the present invention was founded yet failed to recognize its value in selecting prodrugs with enhanced efficacy.

The rejection of claims 1-5, 9 and 14-16 over Glazier et al. are believed to be moot in light of the claim amendment and the points noted above.

Claims 1 -18 were rejected under 35 U.S.C. 103(a) as being unpatentable over Glazier et al. in view of Starrett et al. The examiner correctly notes that Glazier et al. fails to teach or suggest (a) phosphonester, phosphonoamidate or mixed phosphonoester/phosphonoamidates, (b) aryl esters, (c) amino acid amidates, (d) target and non-target tissues in an intact animal, or (e) assaying a drug metabolite as a measure of activity. According to the examiner Starrett et al. teaches aryl esters, phosphonoamidates, teaches assaying metabolites, and discloses certain anti-tumor activity of PMEA. Starrett et al. are not properly combined with Glazier et al., but even if properly combined, Starrett et al. would not make up for the deficiencies of Glazier et al. Principally, Starrett et al. fails to suggest any reason for Glazier et al. to look at effect of a screened prodrug on different tissues as opposed to simply assaying the prodrug against infected and uninfected tissues of the same type.

In addition, Starrett et al. would fail to teach or suggest any motivation for Glazier et al. to choose anything other than a prodrug in which the hydroxyl group on phosphorus is substituted with "A", a benzyl-oxy derivative with one or more acyl-oxy groups in ortho or para position (col. 4, lines 45-53). Thus, the combination of references is devoid of any amidate prodrugs, including amino acid amidates (Claim 7). The combination also is devoid of any teaching to select relative activity of greater than 10 times in

different tissues (Claim 9), and fails to teach anything about assaying the prodrug or its metabolites in different tissues from an animal to whom the prodrug has been administered (claim 10, 11, 12, 13). It is clear that Glazier et al. would not have considered assaying different tissues from a live animal because he conducted assays in an animal yet failed to appreciate or recognize the invention here, and Starrett et al. teach or suggest nothing to the contrary. Starrett et al. fails to supplement the deficiencies of Glazier et al. The examiner is requested to reconsider and withdraw this rejection.

This application is now believed to be in condition for allowance. An early Notice to that effect is solicited.

Respectfully Submitted,

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